

# Clinical Investigation

## Antibiotic-Associated Colitis

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*We determined the incidence of antibiotic-associated colitis among users of oral antibiotics or topical clindamycin in a large prepaid health plan. Exposure to antibiotics was determined using a system that automatically records outpatient prescriptions filled and hospital diagnoses were available from computer files. Four cases of acute colitis were judged likely to be causally linked with outpatient use of antibiotics. These findings provide substantial evidence that antibiotic-associated colitis requiring hospital treatment occurs very rarely.*

(Stergachis A, Perera DR, Schnell MM, et al: Antibiotic-associated colitis [Clinical Investigation]. West J Med 1984 Feb; 140:217-219.)

Certain drugs have been implicated in the development of colitis. Most notably, pseudomembranous colitis has been reported after systemic therapy with lincomycin, clindamycin hydrochloride, ampicillin, erythromycin ethylsuccinate, tetracycline hydrochloride and cephalosporins.<sup>1-4</sup> Recently, several cases of pseudomembranous colitis after topical application of clindamycin hydrochloride for acne vulgaris were reported.<sup>5,6</sup> We report on the relationship of orally given antibiotics and topical clindamycin used in the outpatient setting and newly diagnosed colitis leading to admission to hospital. The study encompassed a large, defined outpatient population and their hospital experience.

### Patients and Methods

The Group Health Cooperative of Puget Sound is a consumer-owned cooperative founded in Seattle in 1947. As of January 1, 1980, there were about 280,000 members. The plan provides comprehensive prepaid medical coverage for outpatient care, drugs and hospital services. The vast majority of drugs are provided free of charge for most of the membership and at a reduced cost for the rest. With few exceptions, members are admitted to hospitals in the Seattle area maintained by the Cooperative.

Information on all discharges from Group Health hospitals has been recorded and placed on computer files by the Commission on Professional and Hospital

Activities-Professional Activity Study (CPHA-PAS) in Ann Arbor, Michigan, since 1972. This information includes hospital discharge diagnoses and the surgical procedures done, together with routine demographic data. These records provide ready identification of persons with colitis-related disorders.

In July 1975 the Cooperative began to computerize records of all prescriptions filled in its regional outpatient pharmacies. This process was accomplished in stages by phasing in one regional pharmacy at a time, and was completed by July 1, 1976. Of some 500 women interviewed in previous studies of this population, 98% stated that they routinely used the Group Health pharmacies to fill their prescriptions.<sup>7</sup> Also, among 387 persons interviewed in a recent study, it was reported that 90% of their prescriptions were obtained from Group Health pharmacies. Thus, the outpatient drug-use records, including dates, of virtually all members are accessible in machine-readable form and can be readily linked to hospital care information. The availability of detailed information on drug use in a defined population enabled us to calculate the incidence of colitis among those who received drugs of interest.

From the CPHA-PAS files we identified 344 persons with a hospital discharge diagnosis of colitis (Hospital-International Classification of Diseases Adapted [H-ICDA] codes 563, 563.1, 563.2, 563.9, 564.1, 564.9)

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Submitted, revised, September 19, 1983.

The Boston Collaborative Drug Surveillance Program is supported in part by the Food and Drug Administration (Cooperative Agreement 1 U01 FD 01223-01).

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between 1977 and 1980. Excluded from further study were eight persons who had been members of the Group Health Cooperative for less than six months because the history of recent drug use and past history were insufficient. Also excluded from further evaluation were 120 persons in whom colitis was a secondary diagnosis unrelated to the primary reason for admission to hospital. An additional 115 persons were excluded because the record indicated that they had had chronic colitis before the admission under study. Patients who had chronic colitis were defined as those with previous admissions for colitis or those receiving sulfasalazine before the admission.

There remained 101 persons admitted to the hospital for the first time (according to our records) for acute colitis. For these patients, the entire clinical record was sought and reviewed to determine the reason for the admission to hospital.

Four medical records could not be found. In addition, 90 more cases were excluded from the study because the medical records showed a diagnosis or other evidence of Crohn's disease, functional bowel disorders or chronic colitis. There remained 11 patients admitted to hospital for the first time for acute colitis.

## Results

Four of the 11 patients with acute colitis had received antibiotics by mouth as outpatients just before symptoms developed. The other seven cases did not receive antibiotic therapy within three months of symptoms developing. Details of each of the four cases are given below.

### Reports of Cases

**CASE 1.** The patient, a 34-year-old woman with no past history of colitis, was started on a regimen of dicloxacillin sodium, 1 gram a day, for a toe infection. She had severe lower abdominal pain and crampy pain a week after starting the therapy. She was subsequently admitted to hospital after three weeks of crampy lower abdominal pain. During the hospital stay, sigmoidoscopy showed unusual colitis with patches of adherent whitish plaques. Rectal biopsy findings were typical of pseudomembranous colitis. The discharge diagnosis was pseudomembranous colitis due to dicloxacillin administration. She was given a course of vancomycin and no further colitis-related problems were reported during the following period.

**CASE 2.** The patient was a 38-year-old man with no previous history of colitis. Ampicillin was prescribed, 2 grams a day for seven days, for acute epididymitis. Two days after starting the ampicillin regimen, he had abdominal cramping and loose stools with some blood mixed in them. He was admitted to hospital five days after onset of the abdominal symptoms. The patient had a normal leukocyte count and was afebrile on admission. Laboratory investigation during the hospital course showed no ova, parasites, *Shigella* or *Salmonella* in the stool cultures. Sigmoidoscopy showed that the sigmoid mucosa was somewhat granular and red but not bleed-

TABLE 1.—Rate of Cases of Antibiotic-Associated Colitis at Group Health Cooperative of Puget Sound (Seattle), 1977-1980

Antibiotic	Persons Receiving Drug Number	Cases of Colitis Among Users Number	Rate Per 100,000 Persons
Dicloxacillin sodium ..	34,315	1	2.9
Tetracycline			
hydrochloride .....	72,684	2	2.6
Ampicillin .....	63,518	1	1.6
Penicillin .....	97,255	0	0
Erythromycin			
ethylsuccinate .....	77,857	0	0
Amoxicillin trihydrate .	18,883	0	0
Cephadrine .....	10,569	0	0
Clindamycin			
hydrochloride .....	1,509	0	0

ing. The patient's bloody diarrhea stopped after admission and he was discharged with a diagnosis of possible antibiotic-induced colitis. There were no further colitis episodes during the follow-up period.

**CASE 3.** The patient, a 34-year-old man, was prescribed a ten-day course of tetracycline, 1 gram per day, for prostatitis. Two weeks later he was given a ten-day course of ampicillin, 1 gram per day, for the same condition. He was admitted to hospital 11 days after starting the ampicillin regimen because of severe crampy lower abdominal pain for ten days. Sigmoidoscopy showed a purulent mucoid exudate coating the wall of the colon and a moderately severe colitis with irregular patchy ulceration. The rectal biopsy specimen showed nonspecific acute and chronic inflammation. Examination of stool specimens was negative for ova and parasites and cultures showed no enteric pathogens. The discharge diagnosis was colitis. Sigmoidoscopy two months after discharge showed that the colitis had completely resolved.

**CASE 4.** The patient, a 21-year-old previously healthy woman, was admitted to hospital with a history of bloody diarrhea for five weeks. One week before the onset of symptoms she was placed on a 25-day regimen of tetracycline, 500 mg a day, and benzoyl peroxide for acne. Sigmoidoscopy done during the hospital course showed a number of shallow ulcerative lesions in the rectal ampulla, more severe distally. The discharge diagnosis was ulcerative colitis. The colitis was quiescent during the follow-up period.

The four antibiotics implicated in the cases reported above and other antibiotics not implicated are shown in Table 1. The estimated incidence of admission to hospital of cases of antibiotic-associated colitis among users of oral ampicillin, dicloxacillin and tetracycline was 1.6, 2.9 and 2.6 per 100,000 persons exposed, respectively. There were no cases of colitis among the 1,509 persons receiving clindamycin topically or orally.

## Discussion

These findings provide substantial evidence that antibiotic-associated colitis requiring hospital treatment occurs very rarely. Only four cases of colitis were judged to be linked with antibiotic use in a population of some

280,000 persons over a four-year period, despite the fact that outpatient antibiotic use in this population was common. Interestingly, two cases were not treated either because the attending physician did not know of the previous antibiotic therapy or because the patient improved with symptomatic treatment. Each of the drugs implicated (ampicillin, doxycycline and tetracycline) has been previously linked to colitis.<sup>1-4</sup> Until now, however, there have been no reported estimates of the incidence of antibiotic-associated colitis in a well-defined population using antibiotics orally or topically as outpatients.

None of the cases of colitis involved topical forms of clindamycin or erythromycin. During the study period, the Group Health Cooperative compounded a 1.2% topical preparation from clindamycin hydrochloride capsules. A total of 1,509 persons received oral or topical clindamycin prescriptions during the study period. Using pharmacy records, we estimated that about 1,124 prescriptions were for the topical form during the study period. The experience with topical clindamycin in the present study at the Group Health Cooperative is too small to rule out a rare instance of colitis from this preparation. However, the data are sufficient to rule out the possibility that this complication is common (lincomycin was not used by this population). About 5.3% of the erythromycin used was in the topical form. All other antibiotics reported in this study were given orally.

The information presented is free of major selection biases because all diagnosed cases of acute colitis in a defined population were identified from preexisting computer files. In addition, recall bias for drug use is avoided by using automated recording of prescriptions refilled and review of the clinical record.

Mild cases of antibiotic-associated colitis that did not require hospital treatment would not be found by our methods. Also, patients who had antibiotic-associated diarrhea without colitis may have been missed. *Clostridium difficile* toxin assays were not routinely available at the time of this study.

The generally reassuring findings reported here do not reduce the need for caution in the outpatient use of antibiotics. All patients receiving antibiotics should be warned to consult their physicians if diarrhea or other intestinal symptoms occur.

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